## ANTICONVULSIVE COMPOSITIONS AND METHOD OF TREATING CONVULSIVE DISORDERS

## BACKGROUND OF THE INVENTION

## 1. Field of the Invention

This invention relates to a group of pharmaceutically acceptable amino-carboxylic acids and their amide derivatives and to pharmaceutical uses for these compounds. More particularly the invention pertains to the use of these compounds as anti-convulsant, sedative and anxiolytic agents in mammals.

## 2. Description of the Prior Art

Certain induced, recurrent, generalized seizures in mammals can be prevented by the administration of glutamine (GLN). These seizures have been thought to be related to the depletion of brain glutamine and its product gamma-amino-butyric acid (GABA), which is known to be a major inhibitory neurotransmitter substance acting between the nerve cells in the brain. Decreased GABA in the brain causes seizures. A precursor of GABA is the amino acid glutamine. GABA itself cannot be used clinically to prevent seizures because it does not cross the blood-brain barrier and has serious side effects (hypotension, shock, mortality). Glutamine is metabolized too quickly to be pharmacologically effective.

Several investigators have indicated that the use of 30 GABA agonists given systemically is not associated with a useful anti-convulsant effect. For example, Meldrum (in an article published in The Lancet, August 5, 1978, at p.304-306) teaches that diffuse activation of GABA receptors by GABA or a GABA agnoist given 35 systemically does not provide a useful anti-convulsant effect. An article by Tsuchiya et.al., in Journal of the Physiological Society of Japan, 22,70-74 (1960) reports on the administration to mice of GABA and deltaamino valeric acid (DAVA) ten minutes before induc- 40 ing convulsions by the application of electroconvulsive shock. The results reported by the authors demonstrate that DAVA is ineffective in preventing or inhibiting convulsions and after initial testing the compound was dropped from subsequent anticonvulsant trials as re- 45 ported in the article.

It has now been unexpectedly discovered that DAVA's anticonvulsant activity is delayed after introduction and administration of DAVA and other related amino-carboxylic acids either as free amino acids or 50 their amide derivatives can be used to prevent seizures in mammals or decrease the severity of convulsive episodes.

It has also been surprisingly found that these amino acid components are useful an anxiolytic agents in mam- 55 mals.

Accordingly, it is an object of the present invention to provide a method of preventing seizures, and particularly epileptic seizures in mammals.

Another object of the present invention is to provide 60 pharmaceutical dosage forms containing amino acid compositions which are analogs of glutamine, thus making more glutamine available for conversion to GABA.

Still another object of the present invention is to provide pharmaceutical formulations comprising an 65 effective amount for inhibiting the onset of seizures of an amino acid composition in a solid or liquid dosage form.

A further object of the present invention is to provide an effective method of administering the anti-convulsant compositions disclosed herein.

A further aspect of the present invention is to provide effective sedative compositions.

These and other aspects of the invention will be apparent from the following description.

Convulsive disorders (e.g. epilepsy, seizures, fits, convulsions) have in common the occurrence of brief episodes. These episodes are associated with loss or disturbance of consciousness. Such episodes are usually but not always associated with characteristic body movements, and sometimes with autonomic hyperactivity. They are generally correlated with abnormal EEG discharges. The etiology of such disorders is varied and includes, e.g., genetic diseases, metabolic dysfunction, tumors and trauma.

The amino acids found to be useful as anti-convulsant and anxiolytic agents in the present invention may be generally described as aliphatic compounds in which the carboxylic acid and primary amine are separated by three or four units constituting a simple or substituted alkane, an ether or thioether, or an amide forming the backbone of a straight or branched chain molecule. The amine and carboxylic acid are either free acids or an amide and/or ester derivative of the acid. The amide and ester forms have been found to facilitate entry of the compound into the brain.

The active compositions of the present invention are represented by the following general formula:

wherein R<sub>1</sub> is H,

A is H, Ch<sub>3</sub>, CH<sub>3</sub>CH<sub>2</sub>—, HO—CH<sub>2</sub>, HO—CH<sub>2</sub>CH<sub>2</sub>, CH<sub>3</sub>OCH<sub>2</sub>— HS—CH<sub>2</sub>—, HS—CH<sub>2</sub>CH<sub>2</sub>—, CH<sub>3</sub>SCH<sub>2</sub>—,

Y is C=O, HC-OH or, CH-A,

Z is CH-A, O, S; or NH only if Y is C=O, and  $R_2$  is -OH, -NH<sub>2</sub> or CH<sub>3</sub>-CH<sub>2</sub>-O-,

N is 0 or 1, and Y is CH—A when N=O; and A+Y+Z include no more than one Oxygen or S

 $A\!+\!Y\!+\!Z$  include no more than one Oxygen or Sulfur atom

The preferred anti-convulsant of the present invention is DAVA or delta aminovaleric (5-aminopentanoic) acid of the formula:

Aside from its anxiolytic and anticonvulsant activity, DAVA and other compounds of the general formula